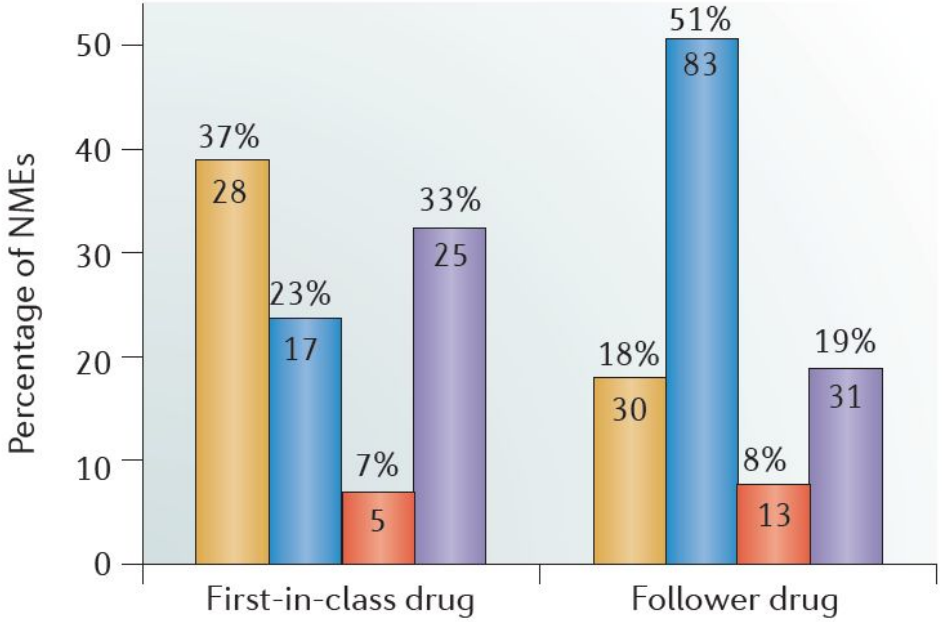
# What can we do if there are no good targets

*Mathematical and Computational Biology in Drug Discovery (MCBDD) Module II*

*Dr. Jitao David Zhang*
*March-April 2021*

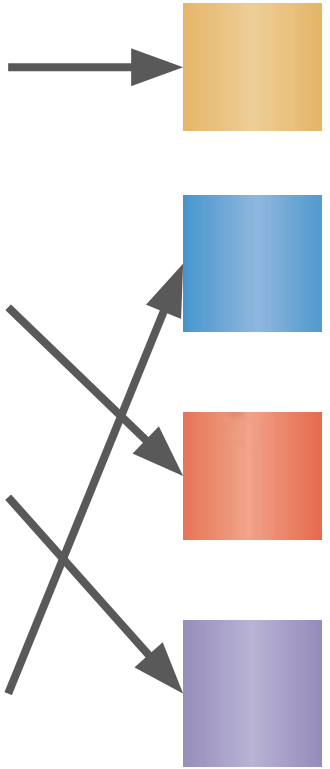
# Five strategies when no good target is found

1. Phenotypic drug discovery
2. Natural products
3. Biologics
4. Interaction-based (multispecific) drug discovery
5. Drug repurposing or combination studies

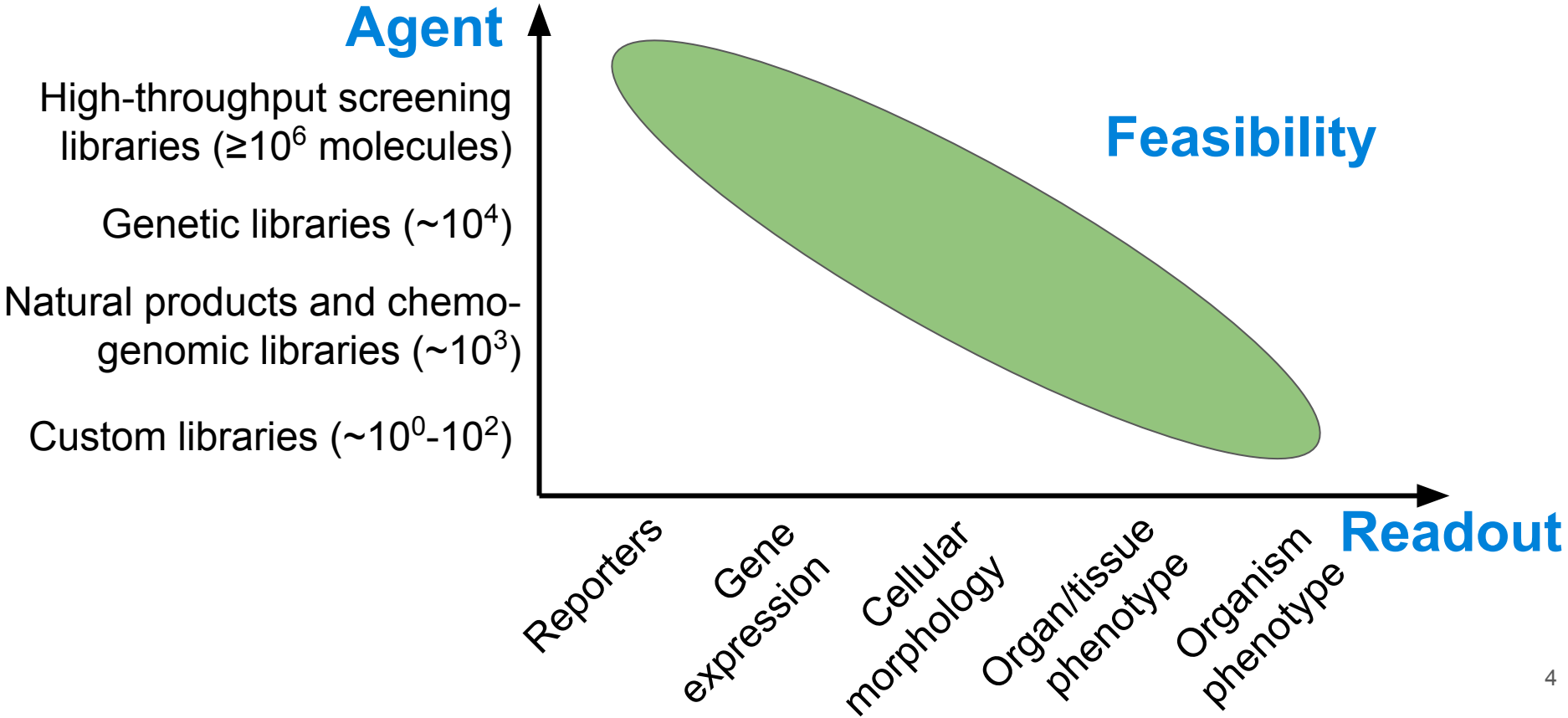



# Connect the lines!

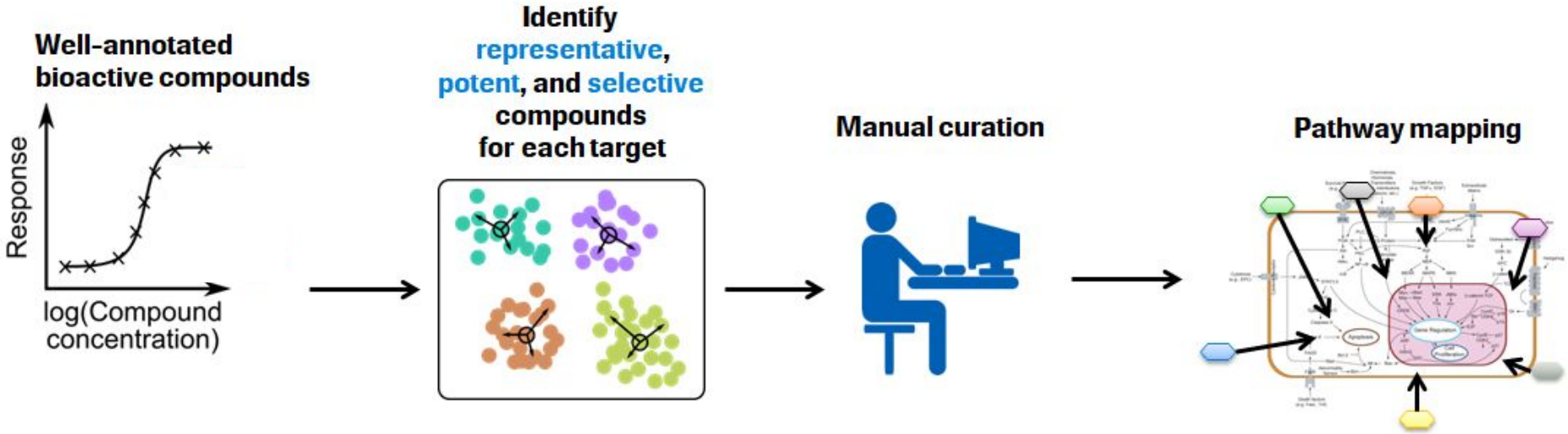
- Phenotypic screening
- Modified natural products
- Biologics
- Target-based screening



# Phenotypic screenings by agent and readout

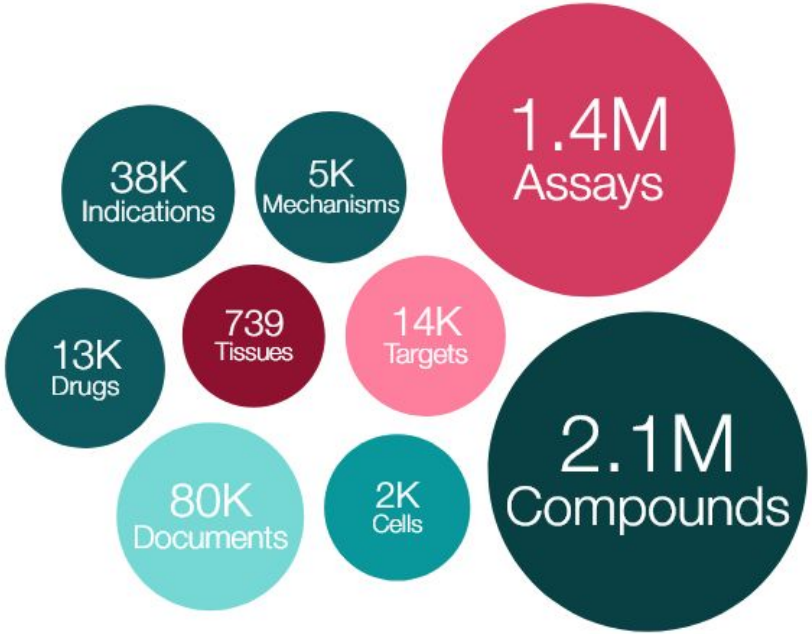


# The Small-molecule PAthway Research Kit (SPARK)



# The ChEMBL database

- An example of query: aspirin.
- Systematic and programmatic accession via ChEMBL API (source code).
- We can use **dose-response data** to annotate the *triplets* of compound, assay activity, and targets.

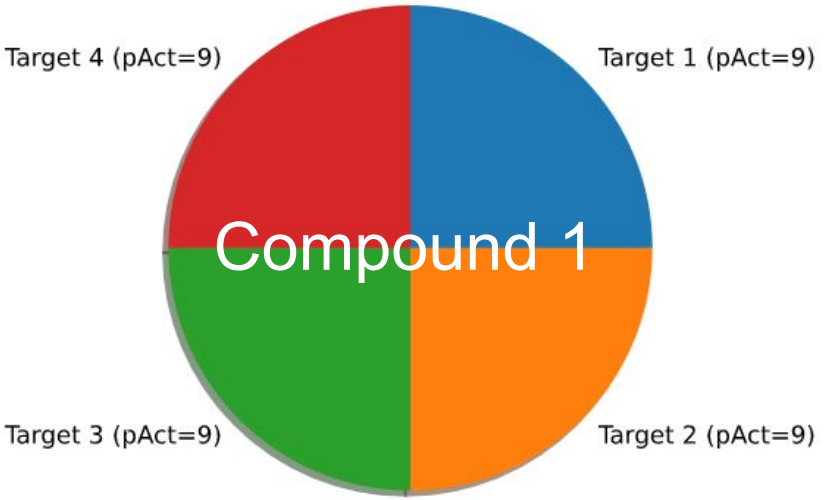


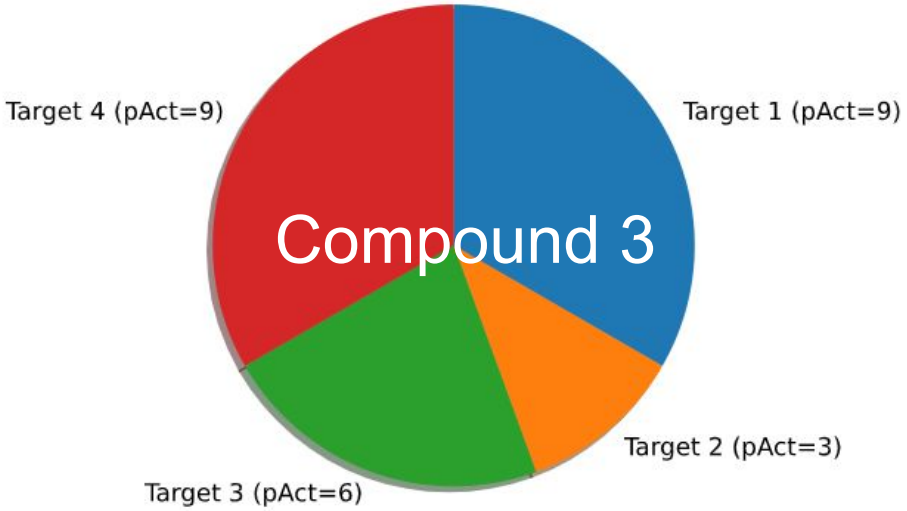

March 2021

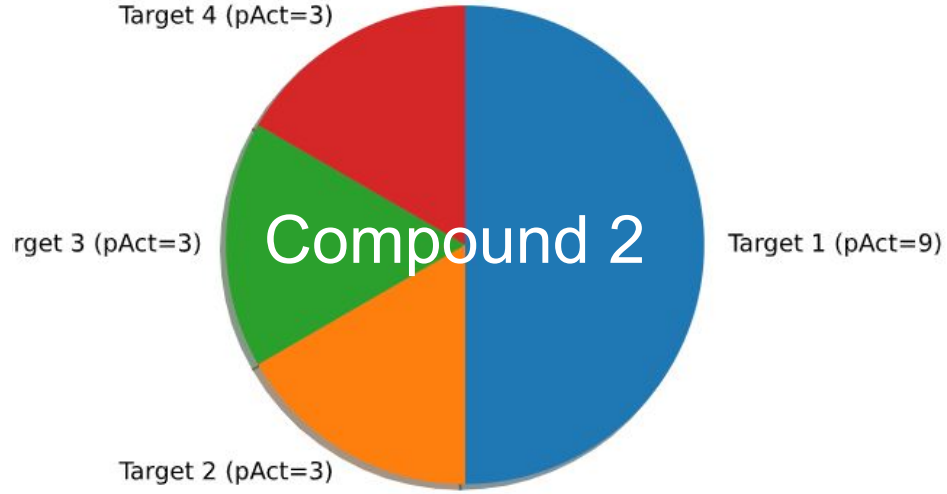
# Discussion

1. Why do we care selecting *representative*, *potent*, and *selective* compounds for each target?
2. How to define following terms mathematically ...
    a. Representativity?
    b. Potency?
    c. Selectivity?

# A toy example about how to quantify a compound's potency and selectivity

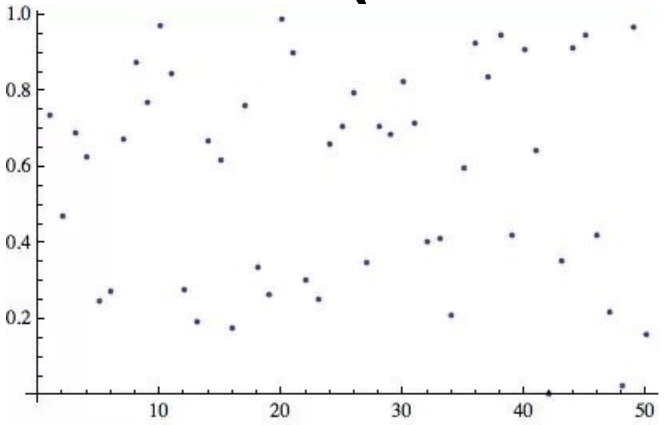


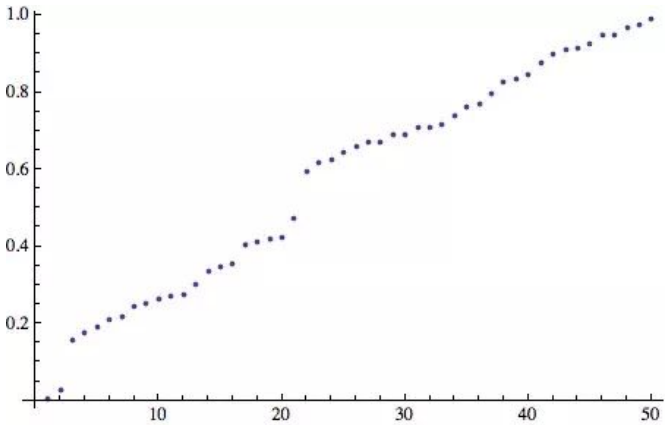



# The Gini Index (Coefficient)

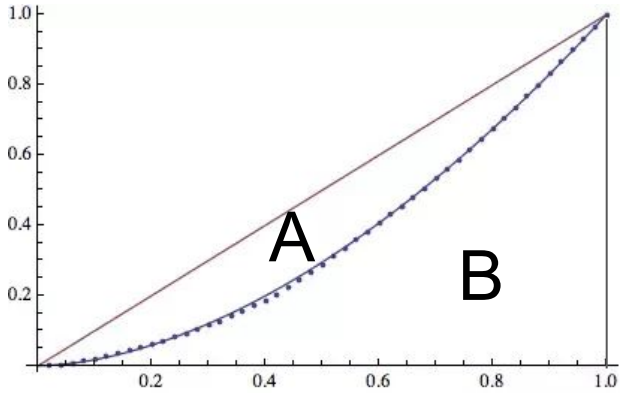
A random vector of 50 values




Sorted from low to high



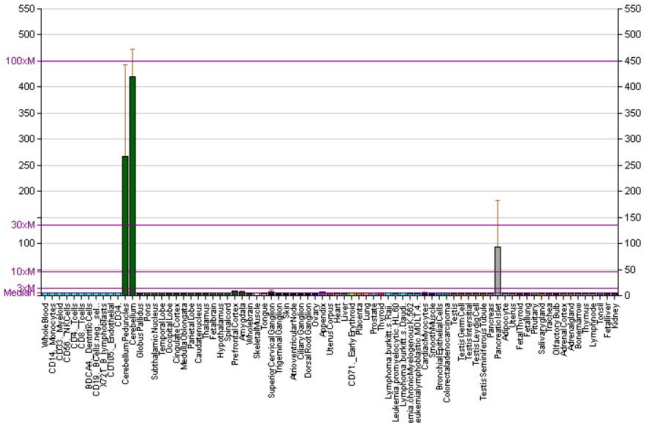

The Gini Index is calculated based on the cumulative distribution



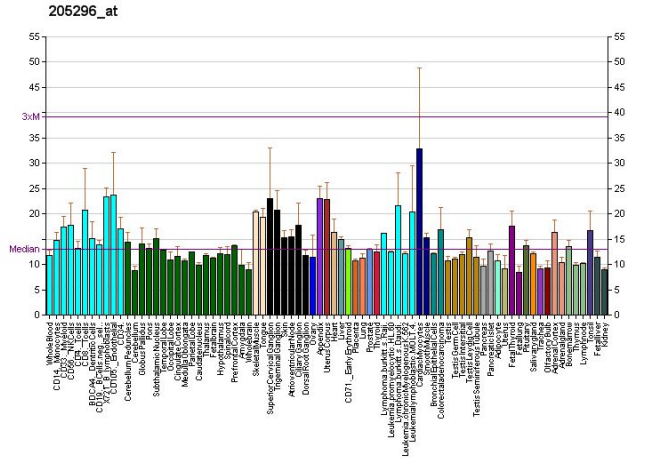

$G=A/(A+B)$

# The Gini Index quantifies inequality/ selectivity

*NEUROD1*

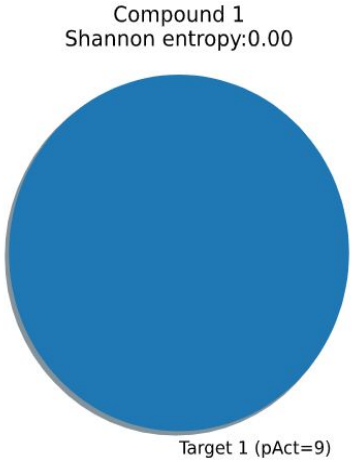


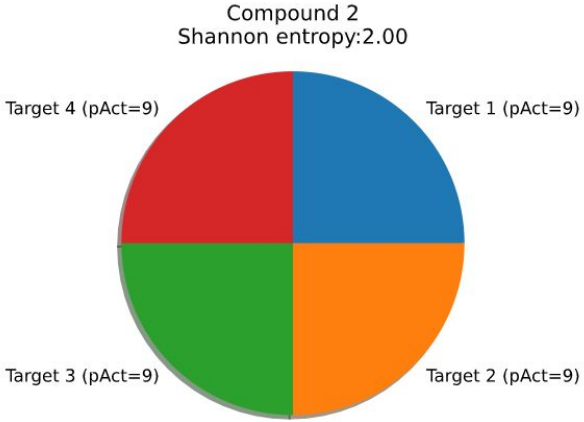

*RBL1*

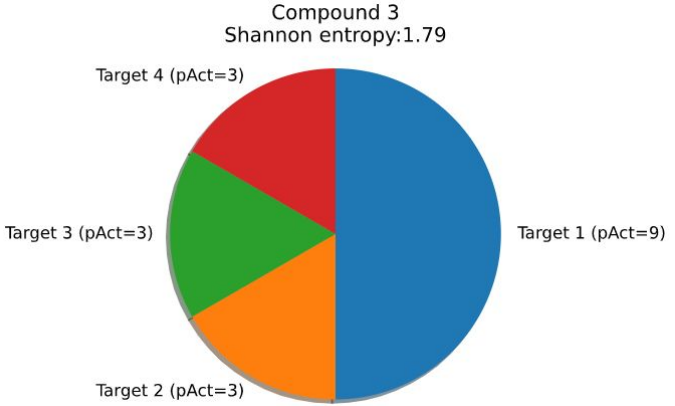


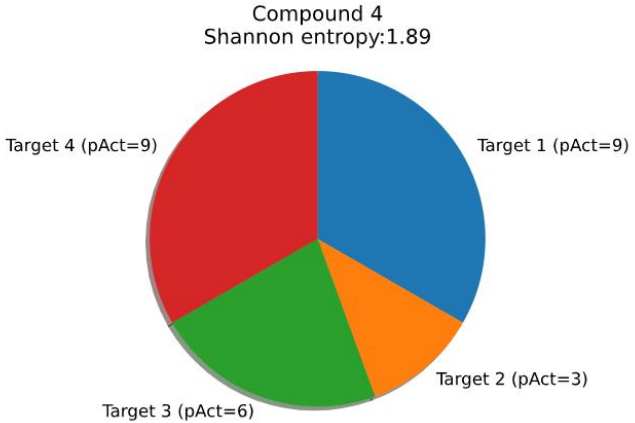

The Gini Index of expression of *NEUROD1* across tissues is near 1, whereas that of *RBL1* is near 0.

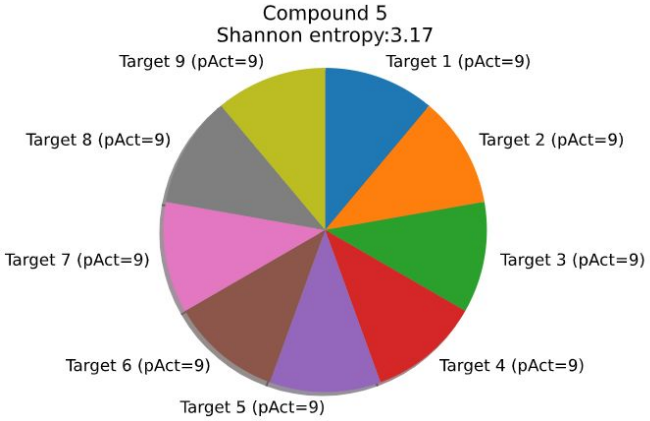
# An alternative metric: Shannon's Entropy



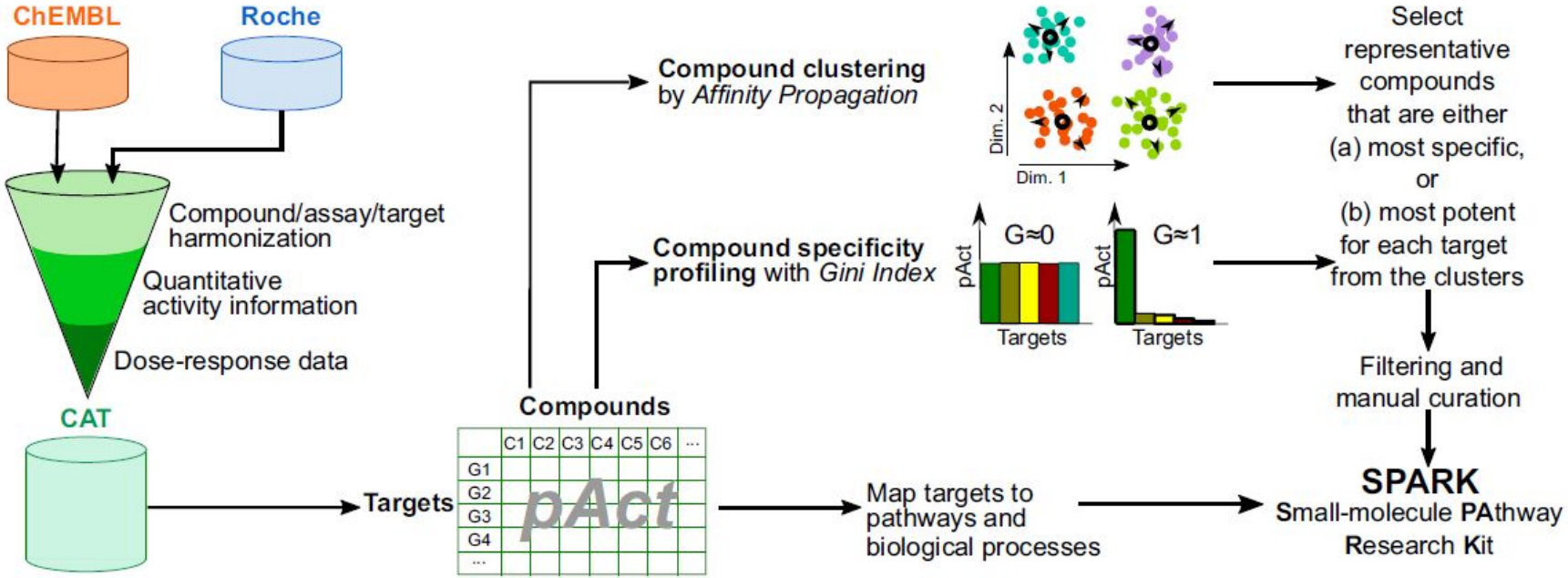



# Construction of SPARK in detail




***Harmonization***

… of public and Roche internal data

***Machine learning***

… to select compounds

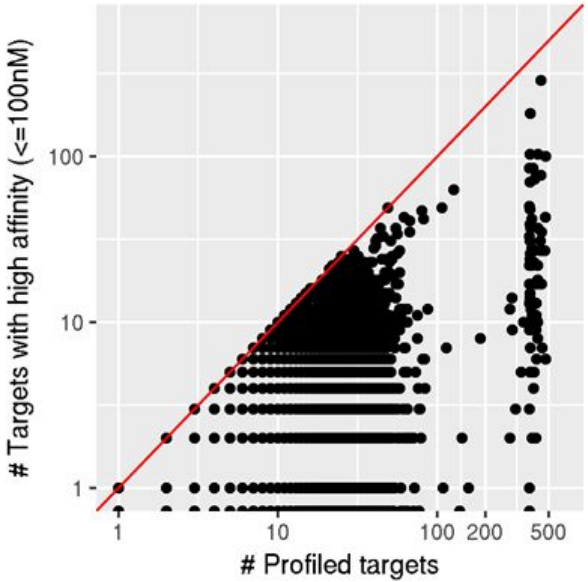
***Pathways***

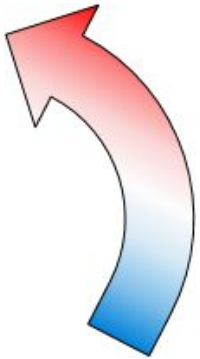
… mapped to compounds

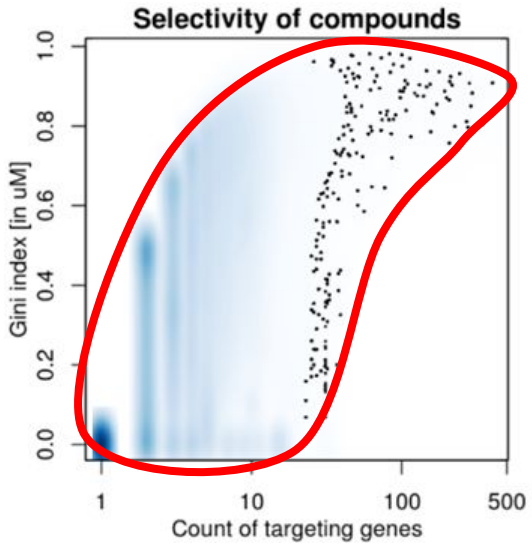
***Curation***

… to enrich quality compounds

# Count of targets and selectivity of ChEMBL molecules



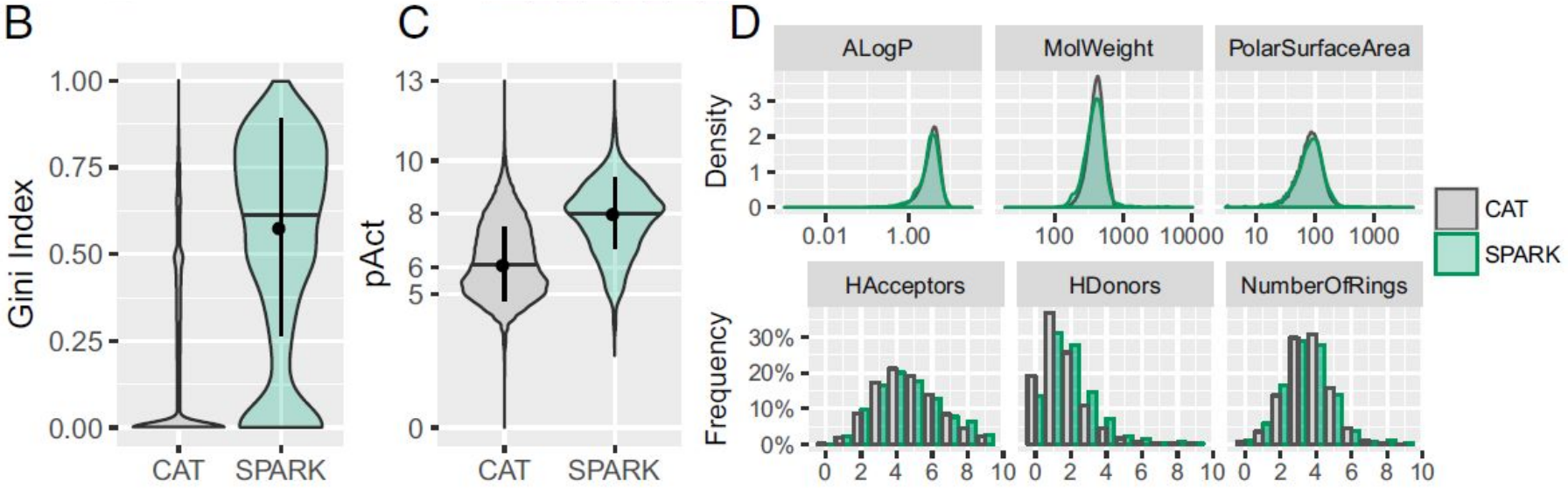



With some exceptions, most compounds are profiled against <100 targets. We distinguish between specific and pleiotropic compounds.

The **shark-fin shape** curve suggests that frequently profiled compounds tend to be more selective (and *vice versa*).

# Unsupervised clustering with Affinity Propagation

# SPARK covers the chemical space evenly with representative, potent, and specific compounds

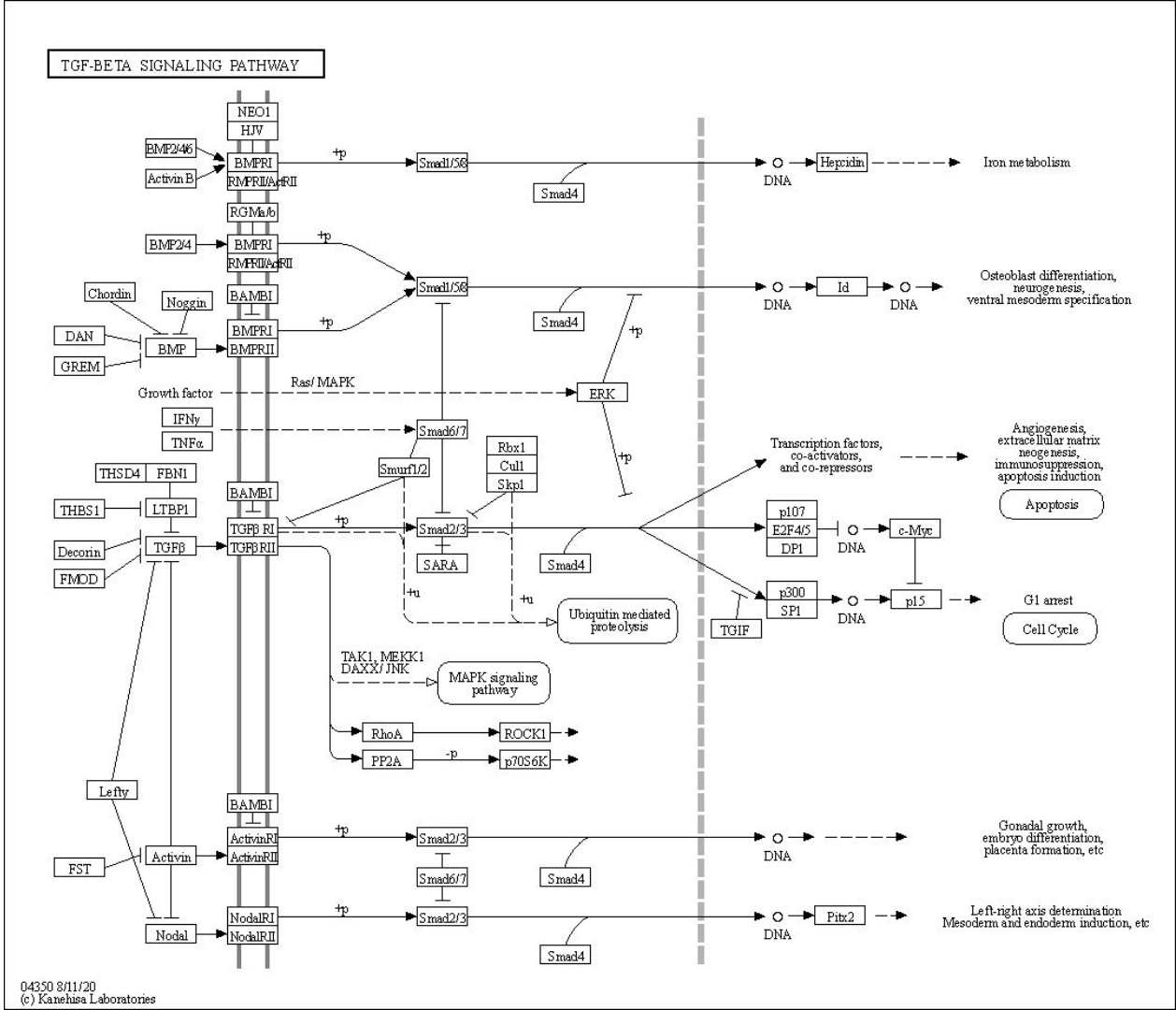



Roudnicky *et al.*, PNAS, 2020, https://www.pnas.org/content/early/2020/08/04/1911532117

# Mapping genes to biological pathways

Option 1: KEGG pathways, with the example of TGF-β signaling pathway.

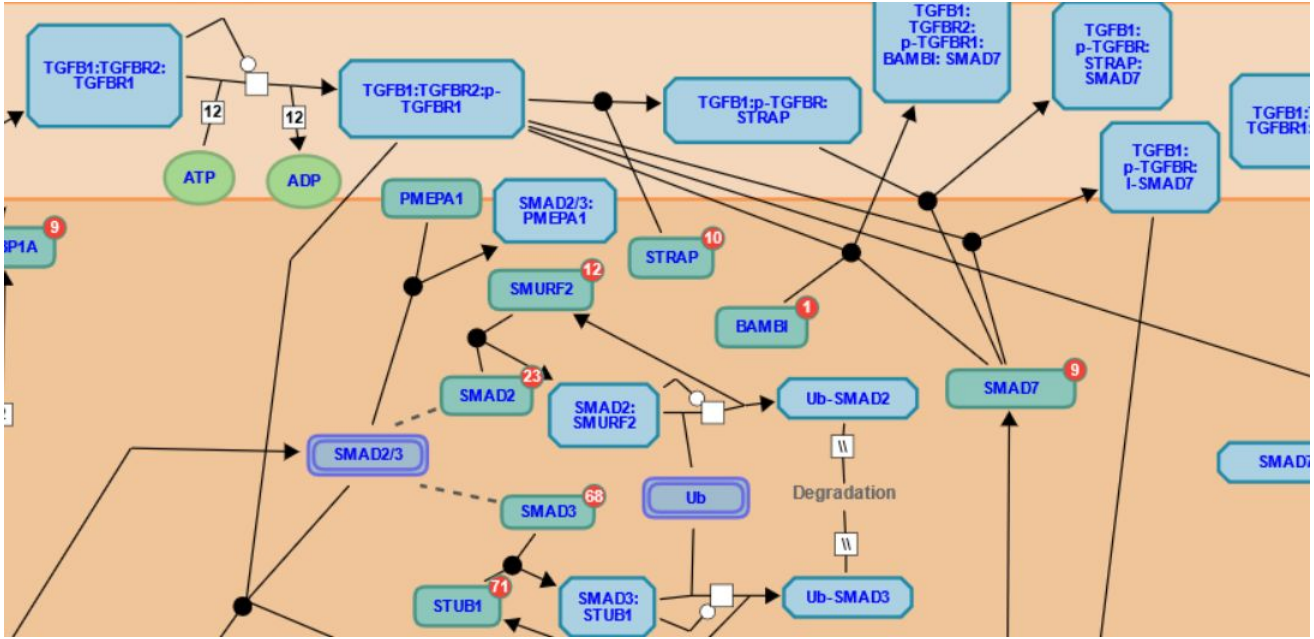
A RESTful API is available for academic use, with clients in Python and R.



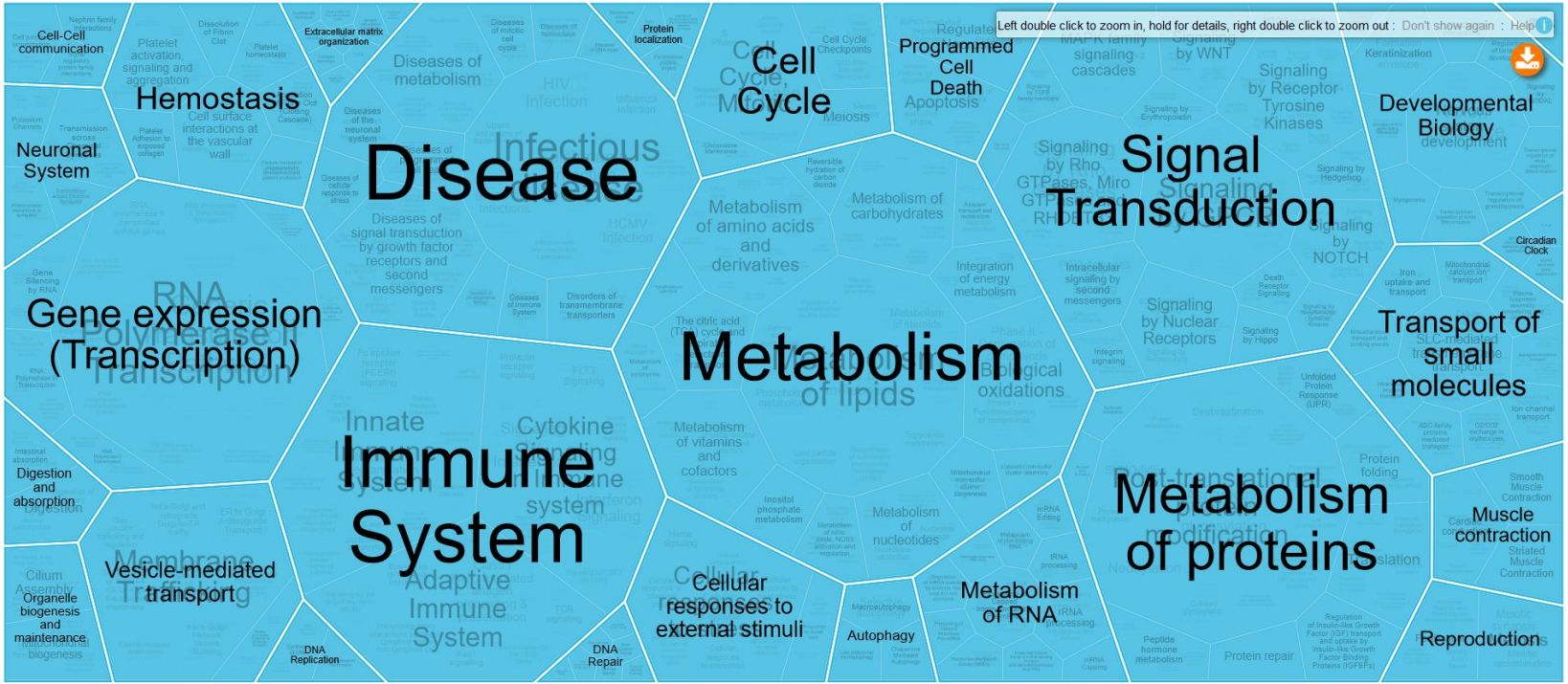
# Mapping genes to biological pathways

Option 2: Reactome pathways, with the example of the TGF-β signaling pathway.

Developer's Zone provides API and graph database interfaces.



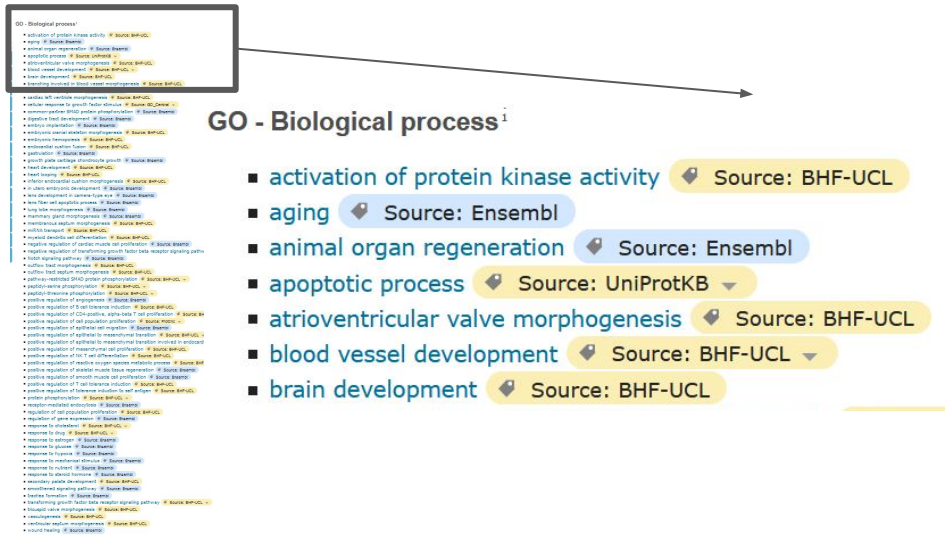
# Overview of pathways captured by Reactome




The Voronoi (Reacfoam) view of all pathways in Reactome

# Mapping genes to biological processes

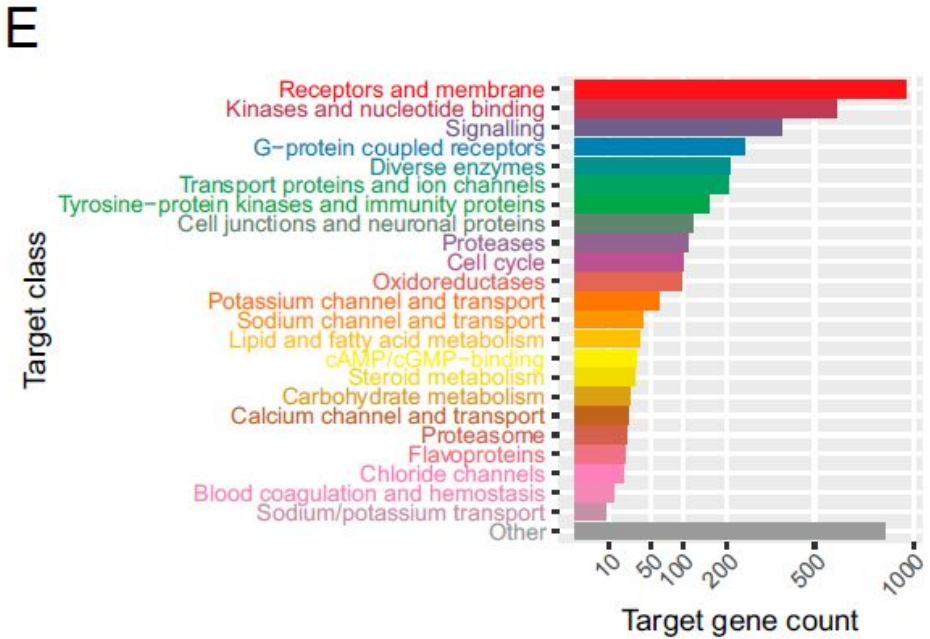
- Gene Ontology
- UniProtKB keywords
- Example: TGFBR2_HUMAN (TGF-beta receptor type -2, P37173)

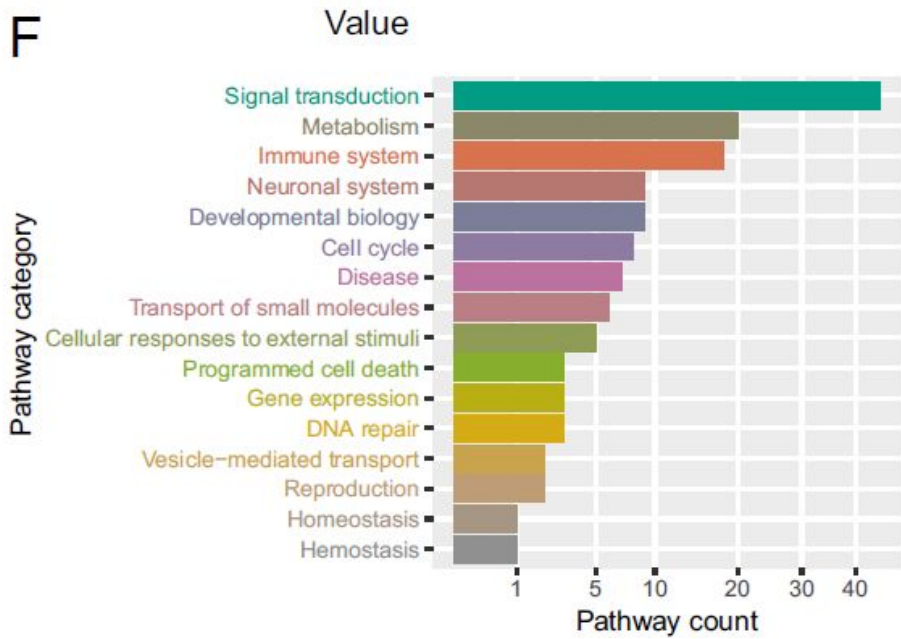



**Keywords**

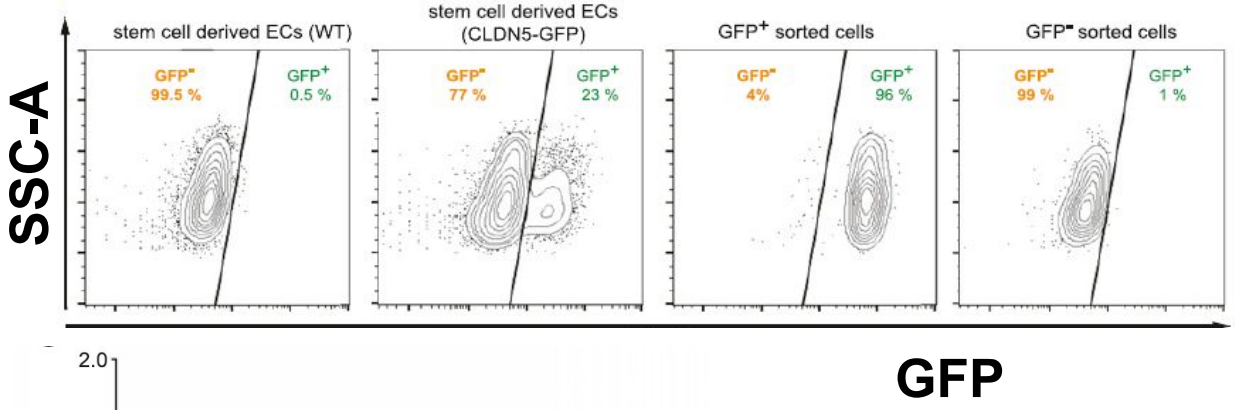
| | |
|---|---|
| Molecular function | Kinase, Receptor, Serine/threonine-protein kinase, Transferase |
| Biological process | Apoptosis, Differentiation, Growth regulation |
| Ligand | ATP-binding, Magnesium, Manganese, Metal-binding, Nucleotide-binding |

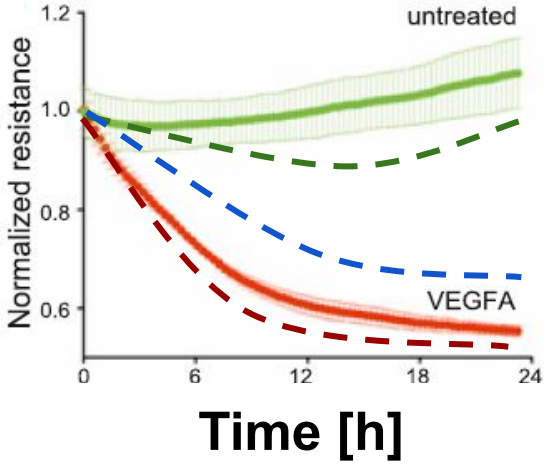
# SPARK covers the target space evenly with representative, potent, and specific compounds

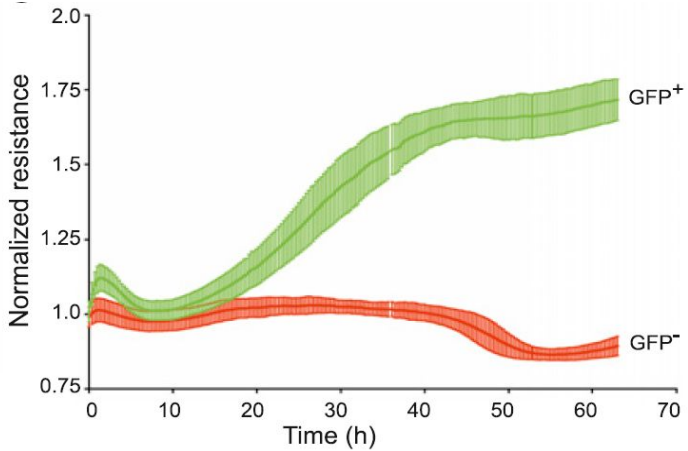


# Screening with stem-cell-derived endothelial cells with a reporter added by genome editing



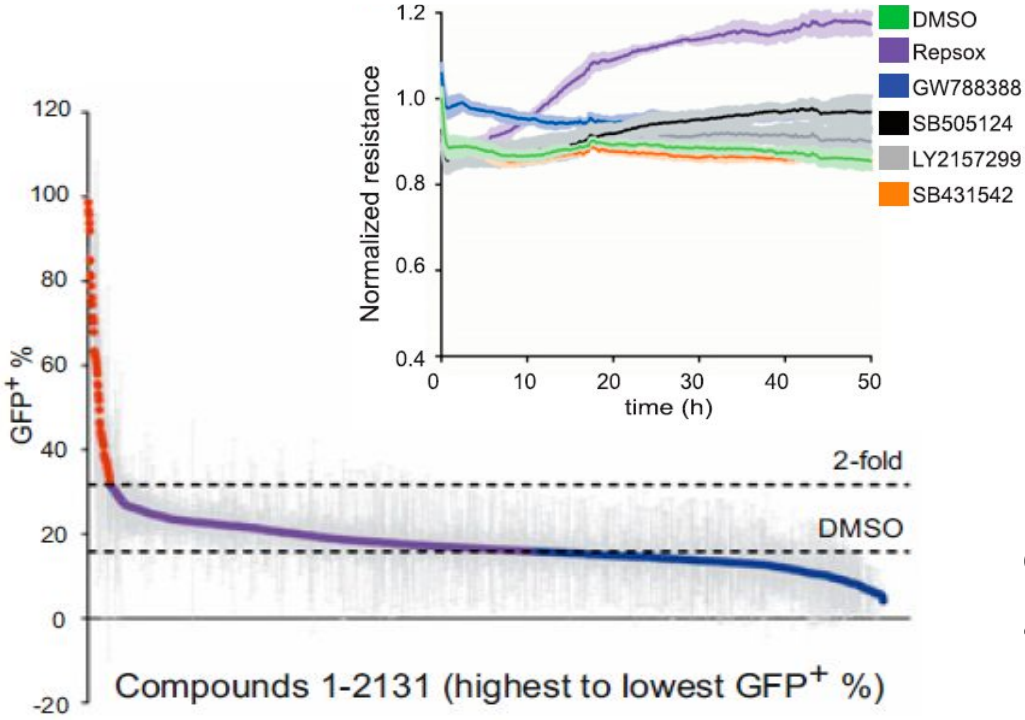




SSC-A: Side-scatter area of flow cytometry;

GFP: Green fluorescent protein;

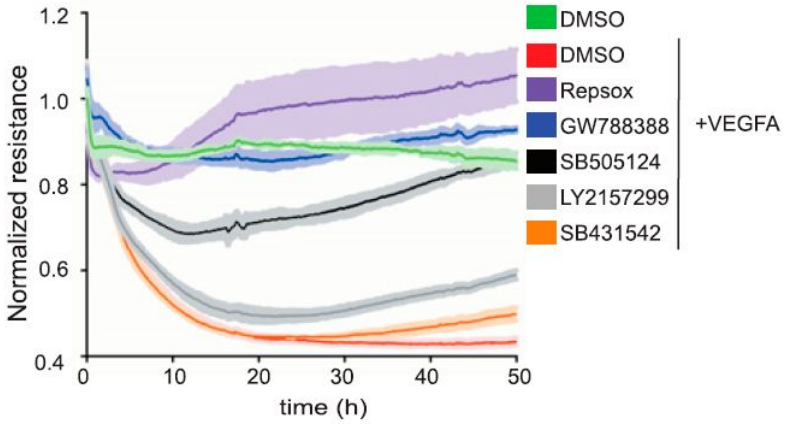
VEGFA: vascular endothelial growth factor A

# Compounds targeting the TGF-β pathway such as RepSox modulates endothelial cells





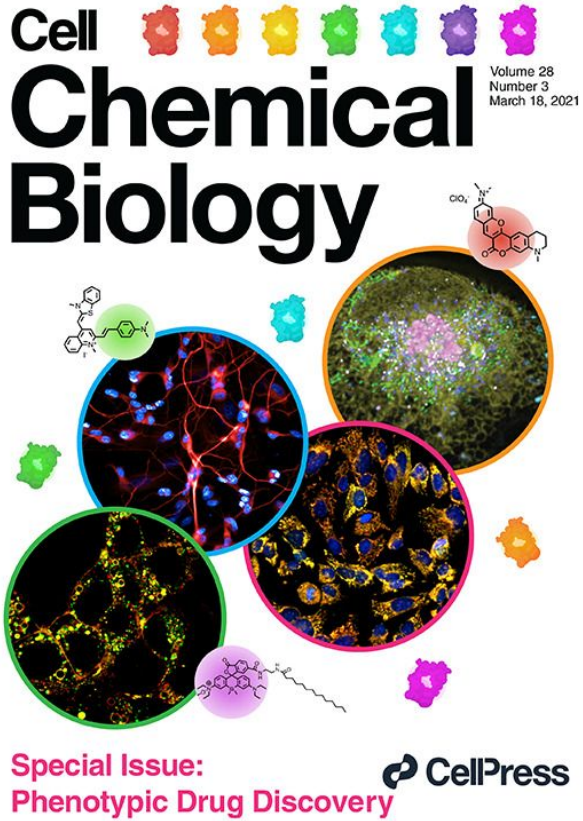





Further *in vitro* and *in vivo* experiments establish RepSox as a tool compound modulating retinopathy.

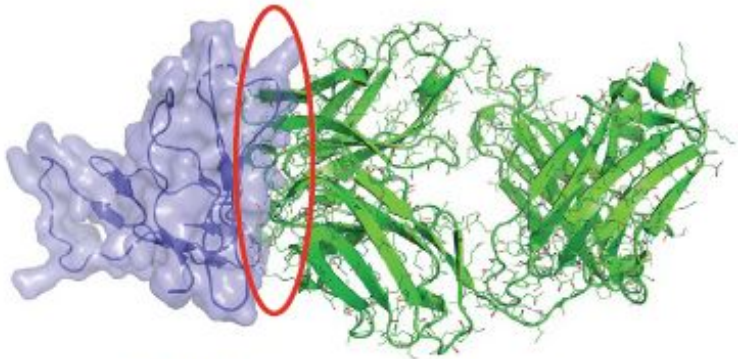
# Conclusions about chemogenomic library

- Phenotypic drug discovery can lead to first-in-class drugs with novel mechanisms;
- Unsupervised machine learning and data modelling contribute to build chemogenomic libraries;
- We can link drug candidates via targets to biological pathways and processes



# Multispecific Drug Use or Target Interactions

**b** Conventional drug:
- Forms 1 drug–target interface
- Can act throughout body
- Only works if its binding to target alters function of target

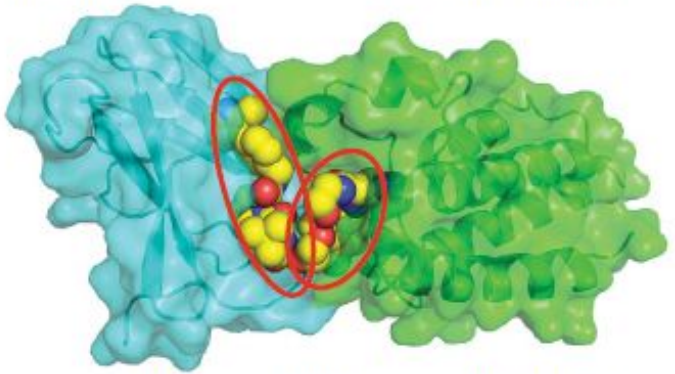


IL-2Rα Basiliximab

**c** Obligate multispecific drug:
- Forms 2 or more drug–target interfaces

Class 1 'tetherbodies'
- Enrich drug at relevant site of action

Class 2 'matchmakers'
- Link drug to a biological effector



VHL MZ1 $BRD4^{BD2}$

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